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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,554	10/06/2000	John F. Engelhardt	875.024US1	4157

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EXAMINER	
BLUMEL, BENJAMIN P	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,554	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Benjamin P. Blumel	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 9, 19, 25, 26, 46 and 58-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9, 19, 25, 26, 46 and 58-69* is/are rejected.

7)☒ Claim(s) *9, 62 and 65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant is notified that Benjamin Blumel is now conducting examination of this application. Correspondence information is stated below.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 10, 2006 has been entered.

This Office Action is in response to Applicants remark/argument dated on April 10, 2006. Claims 1, 9, 19, 25, 26, 46 and 58-69 further examined.

Applicant is informed that any rejection/objection not stated below is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 60-62 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et al. (Gene Therapy, 3(5), 437-447, 1996). Doll et al. teaches that different promoters in recombinant adeno associated vectors have different influences over protein production of the same transgene (β-

galactosidase). See page 438 Figure 1 and 2nd column, last paragraph. Following the transfection of different host cell lines, the percentage of blue colonies and the activity of the transgene were determined which provided positive for all the promoters/enhancers. However, CMV proved to be the promoter/enhancer of choice since a larger amount of transgene activity was observed. Although Doll et al. does not teach contacting a host cell with two rAAV vectors, one with a promoter/enhancer which regulates transcription of the therapeutic gene in the second vector it would be obvious to adapt the vectors used by Doll et al. to separate the promoter/enhancer from the therapeutic gene and utilize a two vector system for introducing DNA into a host cell. This dual vector system would provide two instant benefits, one being additional packaging space for larger therapeutic genes since the promoter/enhancer is located in a separate vector and a second benefit would be providing for interchangeable vectors based on tissue specific promoters/enhancers or therapeutic gene products.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vectors taught by Doll et al. in order to promote the open reading frame of a therapeutic gene. Given the greater effect the CMV promoter/enhancer on the β-galactosidase gene as compared to the other promoters utilized in Doll et al. it would be obvious to use CMV.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims state that splicing is not required for expression of the gene product in the host cell. However, as stated in Engelhardt et al. (Molecular Therapy, Vol.4 No.4, 2001) recombinant adeno associated virus vectors can be linked together in a host cell through intermolecular concatamerization following co-infection. Engelhardt et al. continues to state, "these approaches have used either endogenous or heterologous intronic sequences to facilitate splicing". See page 385, 1st column, 2nd paragraph of Engelhardt et al. In addition, this concept is visually depicted in figure 1 of Engelhardt et al. under "Intermolecular Concatamer Formation". Therefore, it appears that splicing would occur. The specification does not teach how to prevent this, so undue experimentation.

Claims 25, 26, 68 and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors (MPEP 2164.01).

Nature of the invention. The claims are drawn to a method of transferring two recombinant DNA molecules into a host cell.

State of the prior art. At the time the invention was made, successful implementation of transferring multiple DNA molecules into a host cell was a routine practice for those skilled in the art. However, the effectiveness of the unique composition of the two rAAV molecules has not been documented to be a success in the scientific arena nor in the specification of this application. The applicants claim the one rAAV molecule and its promoter will link once inside of the host cell with the another rAAV molecule through an event known as concatamerization. However, due to a lack of published success, and low frequency of recombination events (as stated in Capecchi M. Science, Vol. 244, 1989, pp. 1288-1292) the frequency of a desired homologous recombination event ranges from 1 event in 5,000,000 to 50,000,000) one skilled in the art would have great difficulty obtaining the desired product, especially with no means for selection.

Breadth of the claims. The claims are very broad, covering a method of transferring DNA into a host cell by contacting the host cell with the DNA. The claims are not limited to a specific therapeutic gene, promoter, enhancer or host cell.

Working examples. No working example is disclosed in the specification.

Guidance in the specification. The specification provides guidance towards transforming bacterial cells with two different rAAV vectors. These vectors resemble the instant invention except the vectors utilized comprise an

enhancer followed by a selection marker (β-latamase). Therefore, this vector encodes a protein, which is not claimed. Thus, the specification does not disclose the claimed rAAV vectors in a working example and due to the low probability of a recombination event, see above, further guidance is required.

Predictability of the art. The art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant application, Applicants have not disclosed the claimed vectors stated above nor utilized them in a way to convey their functionality. One experiment does utilize a vector with an enhancer plus a selection marker, which is injected into muscle tissue in conjunction with another vector comprised of a transgene. However, in this example, page 89 on lines 8 and 9 of the specification, approximately 4% of rescued clones contained the transgene and a selection marker existing in a recombined vector with the enhancer, which is outside the scope of the claimed invention. This low percentage of rescue speaks to the unpredictable nature of performing the experiment and achieving significant yields when compared with other forms of transforming vectors into host cells.

Amount of experimentation necessary. Additional research is required in order to determine how effective the promoter will be on the transgene once the two vectors are transduced into a host cell. Considering some experimentation has been completed based on the specification one might deduce that the same processes used in the example stated above with the claimed vectors might reveal a working example. However, with out a selection marker the detection of a recombined vector system becomes increasingly harder. Furthermore, the

physical location of the promoter/enhancer in relation to the transgene may cause additional problems with regard to efficiency of the promoter/transgene relationship. In addition, it seems unlikely that a linked vector system will be recovered based on reasons stated above. Applicants have generated a unique method of producing a transgene in vivo but the method has not been proven to be successful.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin P. Blumel whose telephone number is 571-272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BPB

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